Abstract

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Project Title: Discovery of novel allosteric agonists of the M4 muscarinic receptor

Abstract: *DESCRIPTION* (provided by applicant): Evidence suggests that the antipsychotic effects of cholinergic agents may be mediated by the M1 or M4 subtype of muscarinic receptor. The lack of highly selective compounds, however, has made it impossible to definitively determine whether the behavioral and clinical effects of muscarinic agonists are mediated by M1 or M4. Previous attempts to develop agonists and antagonists that are highly selective for specific mAChR subtypes have failed because of the high conservation of the ACh binding site and difficulty in developing compounds that are truly specific. Novel compounds have now been discovered that act at an allosteric site on the M1 receptor rather than the orthosteric ACh-binding site to induce a robust activation of the receptor and provide high receptor subtype specificity [3, 4]. We have been highly successful in the use of high throughput screening technologies for discovery of novel allosteric ligands at multiple other GPCR subtypes. We have now developed a highly sensitive assay for the M4 muscarinic receptor that is suitable for high throughput screening of small molecule libraries for discovery of novel and specific allosteric agonists of this important GPCR. We propose a series of studies in which an M4 expressing cell line will be used by the MLSCN screening network to identify novel agonists. We will then perform rigorous secondary assays to identify compounds that act at sites other than the orthosteric ACh binding site. Finally, we will use database mining and medicinal chemistry approaches to optimize selected compounds for use as laboratory reagents. Lay summary: The M4 muscarinic receptor is postulated to be an important therapeutic target in schizophrenia. We have developed an assay system for high throughput screening to identify compounds with high selectivity for the M4 receptor subtype that act at an allosteric site on the receptor, thus providing increased specificity for this single receptor subtype. It is anticipated that these compounds will provide important tools for the study of muscarinic receptor function in the CNS.

Thesaurus Terms:
High throughput screening, antipsychotic effects, cholinergic agents, M1, M4, muscarinic receptor, allosteric agonist, mAChR, ACh binding site, GPCR, MLSCN, database mining, medicinal chemistry, schizophrenia, CNS

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